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EduCan Trial: Study protocol for a randomized controlled trial on the effectiveness of Pain Neuroscience Education after breast cancer surgery on pain-, physical-, emotional- and work-related functioning

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Abstract

Introduction:

Over the past decades, awareness on the importance of educational interventions in cancer pain management has increased. However, education is often restricted to biomedical pain management instructions. A more modern educational approach, also known as Pain Neuroscience Education (PNE), explains pain from a biopsychosocial perspective. We hypothesize that this more comprehensive educational approach in the early treatment phase of breast cancer will lead to more beneficial effects for cancer pain management. Therefore, the aim of the present study is to investigate the effectiveness of this PNE intervention, in addition to best evidence physical therapy modalities for treatment and prevention of pain-, physical-, emotional-, and work-related functioning after breast cancer surgery, compared to a traditional biomedical educational intervention.

Methods:

A double-blinded randomized controlled trial has been started in November 2017 at the University Hospitals of Leuven. Immediately after breast cancer surgery, all participants (n=184) receive a 12-week intensive standard physical therapy program. They receive three additional refresher sessions at 6, 8 and 12 months post-surgery. In addition, participants receive three educational sessions during the first month post-surgery and three 'booster sessions' at 6, 8 and 12 months post-surgery. In the intervention group, the content of the education sessions is based on the modern PNE approach. Whereas in the control group, the education is based on the traditional biomedical approach. The primary outcome parameter is pain-related disability 1 year after surgery. Secondary outcomes relate to other dimensions of pain and physical-, emotional-, and work-related functioning at 1 week, 4, 6, 8, 12 and 18 months post-surgery.

Ethics and dissemination:

The study will be conducted in accordance with the Declaration of Helsinki. This protocol has been approved by the ethical committee of the University Hospitals of Leuven. Results will be disseminated via peer-reviewed scientific journals and presentations at congresses.

Trial Registration: ClinicalTrials.gov Identifier: NCT03351075

Ethical Committee of the University Hospitals Leuven: s60702

Strengths and limitations of this study

- This study comprises a well-powered clinical trial investigating the additional effect of an easy deliverable Pain Neuroscience Education (PNE) intervention for pain-related disability and related outcomes following breast cancer treatment.
- A strength of the trial is the pragmatic nature of the study and applicability in daily clinical practice.
- The study is powered for the primary outcome parameter 'pain-related disability' 1 year after surgery.

INTRODUCTION

Breast cancer is the most frequent malignancy among women worldwide.(1) Despite the high incidence, in Western countries an increase in survival and life expectancy has been observed due to the ongoing improvement of detection method accuracy, early diagnosis, and breast cancer treatment.(1) Consequently, more attention is warranted towards the debilitating problems accompanying this disease and its treatment, which can persist for months or even years after diagnosis. In addition to fatigue, pain is the most frequent and persistent symptom following cancer and cancer treatment. Between 27 and 79% of women report pain one month after surgery, which is often attributed to local pain mechanisms caused by a post-surgery and/or radiotherapy tissue insult at that time-point. (2-5) One would expect prevalence rate to diminish as healing occurs, yet this does not seem to be the case. In fact, 12-82% of women still report persistent pain one year or later.(4) This may indicate that besides local nociceptive and neuropathic pain mechanisms, a third pain mechanism characterized by altered nociceptive processing without clear evidence of persistent tissue damage causing the activation of peripheral nociceptors (i.e. nociceptive pain) or evidence for disease or lesion of the somatosensory system causing the pain (i.e. neuropathic pain). (17-19) Moreover, pain interferes with pain-, physical-, emotional- and work-related disability and therefore severely prejudices a person's quality of life (QOL) and participation in society.(6-8) Hence, adequate pain management in the early stage of breast cancer treatment is necessary to prevent and improve pain and pain-related disability, both at short- and long-term.

Despite the effectiveness of currently applied physical therapy modalities after breast cancer surgery (such as manual techniques, specific exercises and general exercises), up to 72% of women still experience pain and the resulting disabilities after finishing breast cancer treatment.(9) Over the past decades, awareness on the important role of educational interventions in the management of cancer pain has increased.(10-12) These general educational interventions have been shown to be effective for improving pain severity, self-efficacy and knowledge and attitude to pain and analgesia in cancer patients. However, effect sizes are only moderate and of limited clinical relevance.(10) This can be explained by the fact that these educational interventions mainly focus on tissue and tissue

injury as the source of pain and are often restricted to biomedical pain management instructions and general advice on physical activity and analgesics.(10-12) They focus on explaining treatment side-effects and improving patients' coping strategies. Recently, increased knowledge on pain mechanisms has led to a more modern educational approach, also known as Pain Neuroscience Education (PNE).(13-16) This explains the neurophysiology of chronic pain and the ability of the nervous system to modulate pain experience, as well as the potential influences of sleep, thoughts, feelings and culture, among others, on pain. Thereby, it targets a reconceptualization from a biomedical or structural model to an actual biopsychosocial model of pain. Through the knowledge that pain is often an unreliable indicator of the presence or extent of tissue damage and if patients may become open to exploring broader contributions to pain, pain-related behavior might change by shifting from passive therapy-receiving to active self-management. Increased knowledge of the broad contributions to pain (4), as well as awareness of different pain mechanisms following breast cancer treatment (17-19) provides justification for the integration of PNE in this population. Applying PNE could enhance the effectiveness of the currently applied physical therapy modalities for prevention and treatment of pain and related disabilities after breast cancer treatment, compared to a traditional biomedical educational intervention. Indeed, encouraging people to address emotional, cognitive and broader health-related factors in the early stage of cancer treatment may enhance recovery during and after the treatment. To our knowledge, only one controlled trial investigated the effectiveness of PNE in the early stage of breast cancer treatment.(20) Although the results were very promising for shoulder function, only short-term effects were examined, no randomization was performed and no pain-related or other health-related outcomes were evaluated.

Objectives

The main scientific objective is to examine the effectiveness of PNE, in addition to a standard best evidence physical therapy program, on pain-, physical-, emotional-, and work-related functioning in the early stage of breast cancer treatment, compared to a traditional biomedical educational intervention, up to 1.5 years after surgery (EduCan Trial). This will be performed through a double-blinded randomized controlled trial.

METHODS AND ANALYSIS

Described according to the SPIRIT guidelines (http://www.spirit-statement.org/protocol-version/).

Trial design and study setting

A parallel, two-arm randomized controlled trial with blinding of assessors and physical therapists providing the standard physical therapy program in both arms and masking of the participants. The trial started in November 2017 at the department of Physical Medicine and Rehabilitation of the University Hospitals in Leuven (Belgium). A schedule of the EduCan Trial is provided in Table 1.

Table 1. Schedule of enrolment, interventions, and assessments of the EduCan Trial

	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				
TIMEPOINT	$-t_2$ *preop consult*	$-t_1$ *postop consult*	**0**	t_1 *4 Mo*	t_2 *6 Mo*	t_3 *8 Mo*	t_4 *12 Mo*	t_5 *18 Mo*
ENROLMENT								
Eligibility screen	X							
Informed consent	X							
Randomization			X					
Allocation			X					
INTERVENTIONS								
				Intensive phase	*Maintenance phase*			
Standard PT program (All)		n=184		1-2 sessions /week	1 session	1 session	1 session	
Pain Neuroscience Education (IG)		n=92		3 sessions	1 session	1 session	1 session	
Biomedical Education (CG)		n=92		3 sessions	1 session	1 session	1 session	
ASSESSMENTS								
Pain-related functioning (primary outcome)*	X	X		X	X	X	X	X
Pain-related outcomes*	X	X		X	X	X	X	X
Emotional functioning	X	X		X	X	X	X	X
Physical functioning*		X		X			X	X
Work-related functioning*				X	X	X	X	X

*see Table 2 for details on the content of the different assessments at each point in time
Mo = Months; IG=Intervention Group; CG=Control Group

Patient and public involvement in trial design

One female breast cancer patient and a representative of the National Health Service were consulted during the initial grant preparation and trial set up. The patient representative provided valuable insight into the worries and concerns experienced during cancer treatment. The representative of the National Health service contributed to the design of the study and advised on assessment of work-related functioning outcomes.

Eligibility criteria

Women are eligible to participate in the EduCan Trial if they are scheduled for surgery for breast cancer at the Multidisciplinary Breast Center of the University Hospitals of Leuven. Patients with increased risk of developing pain after breast cancer surgery are included.(21-23) Therefore, inclusion criteria are: 1) diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, 2) scheduled for surgical excision including either axillary lymph node dissection and mastectomy (whether or not in combination with reconstructive surgery) or breast-conserving; or either sentinel node biopsy and mastectomy (whether or not in combination with reconstructive surgery); 3) aged 18 years or older; 4) can comply with the study protocol. Patients with active metastasis are excluded because of the higher risk of mortality.

Participant screening, recruitment and consent.

Participants are identified from scheduled operation lists and screened for eligibility criteria. The initial screening process is undertaken by a member of the research team. Potentially eligible participants are approached and recruited during the *preoperative consult* at the Multidisciplinary Breast Center of the University Hospitals of Leuven. All eligible patients receive an information sheet and the explanation of the study during the preoperative consult. Next, they are asked to have a preoperative baseline measurement for which a separate informed consent exists. Because of ethical and deontological reason patients will not be forced to decide on participation in the complete EduCan Trial at this moment, but initially only for the baseline measurements.

During their *postoperative hospital stay*, a member of the research team will meet the eligible participants again, answer further questions and include them in the further trial if

wanted. Then, a second informed consent is signed for participating in the complete EduCan Trial. The preoperative baseline measurement of non-participating patients will be stored in the medical file of the patient and can be consulted on clinical follow-up appointments to evaluate the recovery of the patient but is not used for research purpose. The participants' flow is summarized in Figure 1.

Allocation and randomization

Therapists and assessors are blinded to the allocation of the treatment groups. The therapists providing the standard physical therapy program will be unaware of the type of education received by the patient (PNE in the intervention group and biomedically-focused education in the control group). Assessors are blinded to the maximal extent possible. With regard to this, patients are asked not to communicate with the assessors about the intervention received. Patients are masked for the allocation to the intervention/control group; they do not know which one is the experimental intervention and which one is the control intervention, however they will of course be aware of the intervention received.

At the end of the trial, the success of assessor blinding will be examined by asking whether the assessor thought the participant had received the experimental or control intervention, including the percentage of certainty (i.e. 50% certainty means a pure guess). The same will be done for patient masking. The research members performing statistical analysis will be blinded as well.

The randomization is computer-generated and is performed by using permuted blocks (size=4). An independent co-worker at the department carries out the randomization to ensure blinding of the research team. The sequence of randomization is determined by the patient's identification number, which she receives after signing informed consent. Participants are randomized in a 1:1 ratio between intervention and control arms.

Interventions

Standard physical therapy program

All participants in the EduCan Trial attend a standard physical therapy program. The standard physical therapy program is based on currently available evidence and clinical experience of the research team and will include three physical therapy modalities. First, **manual techniques** including (a) passive mobilizations to restore shoulder range of motion, (b) stretching of the pectoral muscles to improve muscle flexibility and (c) scar tissue massage to improve flexibility of the scar(s) will be implemented.(9, 24, 25) Second, **specific exercises** to improve shoulder range of motion and upper limb strength have been proven to be effective for treatment of upper limb problems after breast cancer and will start immediately after surgery as well.(9, 26) Specific exercises are instructed during the individual session and continued at home. Third, patients are advised on **general exercises.**

General exercises should be implemented to increase patient's physical activity level. In general, these recommendations consist of physical activity at a minimum level of moderate intensity over an extended period and can include e.g. running, walking, cycling, swimming, etc.(27, 28)

During month 1-4 an **intensive physical therapy program** is implemented because of the postoperative side-effects. Patients will attend 1-2 individual sessions of 30 minutes per week during the intensive phase, starting one week post-surgery. All patients start with a frequency of two sessions per week, decreasing to once each two weeks. The decrease in frequency of the sessions is pragmatically chosen based on the individual progression and need of the patient.

Up to one year after surgery a **maintenance physical therapy program** is implemented to follow-up on the exercises performed at home and to treat possible additional/ new side-effects of other adjuvant treatment modalities such as radiotherapy, chemotherapy and hormone therapy. An individual maintenance session of 30 minutes is scheduled 6, 8 and 12 months post-surgery.

Additionally, **information about prevention of lymphedema** is given by a specialized physical therapist: about normal use of the upper limb, avoiding pinching off the arm, skin care and control of body weight.(29) One group information sessions of 60 minutes on this topic is organised each month which should be attended once by every participant (both patients from the intervention and control group together) and this as soon as possible after surgery. Patients also receive a brochure with this information. If patients develop lymphedema they are additionally referred to the Lymfovenous Center of the University Hospitals of Leuven for further treatment of the lymphedema.

Educational intervention

The educational sessions are individual and last for 30 minutes. The first PNE session is given within the first postoperative week before the start of the standard physical therapy program to prepare the patient for the physical therapy sessions. Information is presented verbally (explanation by the therapist) and in multi-media forms (power point presentation with summaries, pictures, metaphors and diagrams on computer). After the first session,

patients also receive an information leaflet on paper and are asked to read it carefully at home. They also receive a web-link to an online presentation that summarizes the provided information. Additional written information that can be read afterwards is a valuable and essential part of the educational intervention. In the following 4 weeks after surgery, 2 additional PNE sessions are provided to ensure that the patient understands the pain physiology and principles of activity management and can relate this to the physical therapy program and his/her pain complaint. However, education is a continuous process initiated at the start and continuing into and followed-up during the longer-term rehabilitation program. Therefore, three additional booster sessions are organized at 6, 8 and 12 months post-surgery. During the booster sessions, the information given postoperatively will be rehearsed and application of the information into future stages of the recovery process will be discussed. Special attention is given to return to preoperative activities and return to work (if applicable). Regarding this, a second information leaflet on paper will be given to the patient. Patients in the control arm and intervention arm will have the same schedule of educational sessions, only the content of the education differs from the intervention arm.

Intervention arm: Pain Neuroscience Education (PNE)

Based on the available literature a modern PNE program has been established to *explain pain* specifically for this population.(10, 12, 20) The content and pictures of the educational sessions are based on the book 'Explain Pain' (Butler & Moseley, 2003), 'Pijneducatie een praktische handleiding voor (para)medici' (Van Wilgen & Nijs, 2011) and the 'The Pain Toolkit' (Peter Moore, 2002), as used in earlier studies.(30, 31) Topics addressed during the PNE sessions will include: the characteristics of acute versus chronic pain; specific side effects of the different breast cancer treatment modalities in relation to pain; how pain is a product of the brain; how pain becomes chronic (plasticity of the nervous system, modulation, modification, central sensitization); potential sustaining factors of pain such as emotions, stress, pain cognitions, and pain behavior.

Additionally, this PNE intervention includes advice for *activity management*, while experiencing pain and other symptoms. In addition to the general recommendations for general exercise and advice to stay active in the standard physical therapy program, the PNE guides patients in performing general exercises and activities according to the graded activity principle. Graded activity is applied according to the guidelines reported by the

International Association for the Study of Pain (IASP).(32) This includes general exercise activities according to pacing strategies for 'persisters' (i.e. restructuring the activity pattern to avoid peaks of over activity and exacerbations of their pain) and graded activity for 'avoiders' (i.e. time-contingent increase of physical activity). PNE is crucial here to help patients interpret pain during exercise in the correct context. Finally, advice on *returning to work* in the context of present pain complaints and how to apply the principles described above for activity management can be applied in the working situation will be provided.

Control arm: Traditional biomedical education

Traditional biomedical educational interventions consist of *explaining patient's pain* experience in relation to the therapeutic procedures from a tissue and biomechanical perspective.(33, 34) Information on the different side effects of surgery, radiotherapy, chemotherapy, hormone therapy and target therapy is given. The role of different structures and injured versus healthy tissue in acute and persistent pain is discussed. Pain is explained from a biomechanical point of view, e.g. deviance from normal expected movement patterns and postures. Additionally, during the educational sessions and rehabilitation program, patients receive advice on activity management. This advice is to stay active as minimally possible during treatment and increase their *physical activity* level according to current recommendations for general exercises after treatment. Based on the American Cancer Society Guidelines on Physical Activity at least 150 minutes of moderate intensity (heart rate 50 to 70% of the maximum heart rate or a score of 12-14 on Borg Rating of Perceived Exertion (RPE)) or 75 minutes of vigorous intensity activity (70 to 85% of the maximum heart rate or RPE of > 15) each week (or a combination of these), preferably spread throughout the week is recommended. Finally, *advice on returning to work* in the context of the different (persistent) side-effects of the treatments will be provided.

Outcomes

The outcome measures were chosen in accordance with the guideline for **core outcome domains** to be used in clinical trials on multimodal treatment approaches for pain as advocated by an international steering committee (**VAPAIN recommendations**)(35) and the **IMMPACT recommendations** for the outcome measures in pain clinical trials.(36)

The primary outcome is pain-related functioning at 12 months measured using the Pain Disability Index (PDI). Secondary outcomes are other pain symptoms and characteristics, physical functioning, emotional functioning and work-related functioning. Assessments are performed within one week preoperatively, within one week postoperatively and then at 4 months, 6, 8, 12 and 18 months after surgery. However, because of feasibility limitations not all outcome parameters are assessed at each assessment time point. Table 1 and 2 present the study outcome measures by assessment time point. In table 3 the outcome measures are described in more detail.

Table 2. Study outcome measures by assessment time point

Domain	**Scale/measure**	**T_{-2} 1W preop**	**T_{-1} 1W postop**	**T_1 4 Mo**	**T_2 6 Mo**	**T_3 8 Mo**	**T_4 12 Mo**	**T_5 18 Mo**
Pain-related functioning (primary outcome)	Pain Disability Index	x	x	x	x	x	x	x
Pain symptoms and characteristics	Pain intensity (VAS)	x	x	x	x	x	x	x
	Brief Pain Inventory (BPI)	x	x	x	x	x	x	x
	Neuropathic Pain Questionnaire (DN4)	x	x	x	x	x	x	x
	Central Sensitisation Questionnaire (CSI)	x	x	x	x	x	x	x
	Pain sensitivity testing	x	x	x	x	x	x	x
Physical functioning	General physical activity level (accelerometry)		x	x			x	x
	Upper limb performance (accelerometry)		x	x			x	x
	Upper limb function (DASH)	x	x	x	x	x	x	x
Emotional functioning	Pain Catastrophizing Scale (PCS)	x	x	x	x	x	x	x
	Depression, Anxiety and Stress Scale (DASS-21)	x	x	x	x	x	x	x
	Health-related quality of life (McGill Quality of life questionnaire)	x	x	x	x	x	x	x
Social functioning	Return to work rate			x	x	x	x	x
	QuickScan			x	x	x	x	x
	Return-to-work self-efficacy (RTWSE-19)			x	x	x	x	x

Table 3. Outcome measures of the EduCan Trial

Outcome	Assessment method
PAIN-RELATED FUNCTIONING (primary outcome)	
Pain-related functioning	Pain Disability Index (PDI). The PDI is a short, self-reported questionnaire for measuring the degree of interference of pain with normal role functioning (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity).(37, 38)
PAIN SYMPTOMS AND CHARACTERISTICS	
Pain intensity	Visual Analogue Scale (VAS). Present pain intensity and mean pain intensity during the past week for pain at the upper limb region (i.e. shoulder-neck region, arm, axilla, trunk side and breast region)
Brief Pain Inventory	Medication use, pain quality, pain location, pain severity and response to treatment.(39)
Presence of neuropathic pain	Douleur Neuropathique en 4 questions (DN4). The DN4 a questionnaire generating reliable and valid data for identifying pain of predominantly neuropathic origin.(40)
Presence of hypersensitivity of the central nervous system	Central Sensitisation Inventory (SCI). The CSI is a questionnaire generating reliable and valid data to assess symptoms related to central sensitization mechanisms.(41)
Pain sensitivity testing	
*- Quantitative Sensory testing: Mechanical detection and pain thresholds**	*Twelve monofilaments (MARSTOCK nerve test - Optihair2, Schriesheim, Germany) with a force from 0.25 to 512 mN are used. The mechanical detection threshold is defined as the lowest mechanical force that the participant can detect. The mechanical pain threshold is defined as the lowest mechanical force that the participant perceives as painful or unpleasant. Monofilaments are applied with a rate of 2 seconds 'on' and 2 seconds 'off' at the inner side of the upper arm and lateral trunk side.*
*- Quantitative Sensory testing: Temperature detection and pain thresholds**	*The computerized thermotest device TSA-II-NeuroSensory Analyser is used. The method of limits is used. The detection and pain thresholds are measured as the first identified stimulus under increasing stimulus intensities. The participant has to push the button once the stimulus is detected or perceived as painful or unpleasant. This is repeated three times for each threshold. The mean of three stimuli for each threshold is calculated and used for analysis.(42).*
*- Quantitative Sensory testing: Pressure Pain Thresholds**	*Measured by a digital Wagner FPX™ algometer. Points of measurement are defined by palpation for most tender muscle points (one per muscle) at the major pectoral muscle region, the lateral trunk side and upper trapezius muscle region. The participant is asked to say 'stop' when the sensation of pressure first changes to pain. The mean value of the 2 measurements is calculated and used for analysis.(43)*
- Presence of widespread pain/secondary hyperalgesia	*Quantitative Sensory Testing is performed both at the local painful area as at remote body parts (i.e. quadriceps muscle at the non-affected side) and pain distribution is displayed on a body diagram*
- Presence and degree of impaired nociceptive inhibitory mechanisms (i.e. conditioned pain	*Assessment of conditioned pain modulation will be done using the Medoc two thermode Q-Sense CPM system. This system involves a 'test' stimulus and a 'conditioning' stimulus applied on the ulnar*

modulation)	*side of the forearms. The test stimulus (at the affected side) is used to assess pain sensitivity to a warmth stimulus pre- and post the noxious conditioning stimulus and the difference is calculated between pre- and post-measures. When the second pressure pain threshold (i.e. test stimulus) is similar or lower than the first, dysfunctional inhibitory pain mechanisms are present.(44, 45)*
- Presence and degree of enhanced facilitation mechanisms (i.e. wind-up)	*Wind-up of pain or temporal summation will be assessed by applying repetitive nociceptive stimulation with a 26g Nylon monofilament at the major pectoral muscle at the affected side. The perceived intensity of the stimulus (the first, the last and aftersensations) are reported by using a Numeric Rating Scale. The temporal summation value is calculated as the difference between the first and the last stimuli or the slope of the increase in pain intensity. A response for enhanced temporal summation is deemed positive if participants perceive the initial stimulus as non-noxious, but it becomes noxious, increasing by at least two-points on a Numeric Rating Scale, or if baseline pain intensity increases by at least two points.(44-46)*
- Presence and degree of hypersensitivity to non-mechanical stimuli	*The Central Sensitization Inventory, a questionnaire generating reliable and valid data to assess symptoms related to central sensitization mechanisms (47-49)*
PHYSICAL FUNCTIONING	
General physical activity and upper limb performance	Three ActiLife accelerometers, one on the pelvis (7 consecutive days) and one on each wrist (3 consecutive days), will be worn during waking hours. Outcome parameters are general activity level, unimanual/bimanual time and intensity of both unimanual/bimanual use. The ActiLife v6.9.5 Firmware v2.2.1 will be used to save raw data. Data will be further processed with Matlab®, using custom-written routines.(50, 51)
Upper limb function	DASH questionnaire. The DASH is a self-reported questionnaire on upper limb function.(3)
EMOTIONAL FUNCTIONING	
Pain catastrophizing	Pain Catastrophizing scale (PCS). The PCS is a self-reported questionnaire measuring catastrophic thinking related to pain. (53)
Depression, anxiety and stress	Depression Anxiety Stress scales 21 (DASS-21). The DASS-21 is a self-reported questionnaire that measures the three related states of depression, anxiety and stress. (54)
Health-related quality of life	McGill Quality of Life questionnaire (55)
SOCIAL FUNCTIONING	
Return to work rate	Self-reported questionnaire on return to work, employment status, work adjustments
QuickScan	Questionnaire on health status and return-to-work obstacles in order to assess potential predictive factors for long-term absenteeism.
Patients perceived ability to work	Return-to-work self-efficacy questionnaire (RTWSE-19). The RTWSE-19 is a self-reported questionnaire on the patients' perceived ability to work.(56)

* Testing is performed bilaterally, except preoperatively because of feasibility reasons

Sample size

A power calculation was performed by the Leuven Biostatistics and statistical bioinformatics Centre of KU Leuven for the primary outcome parameter 'Pain Disability Index (PDI) after 1 year''. Sample size calculation was based on data available in literature for the PDI.(37, 38) and calculated to detect with 80% power a difference of 20% in Pain Disability Index after 1 year. Assuming a coefficient of variation (CV) equal to 0.5, 87 participants per group are needed based on a two-sample pooled t-test of a mean ratio with lognormal data and setting alpha equal to 0.05. The assumed CV is a conservative estimate, derived from the observed CV of 0.30 in a sample of normative data for women with chronic pain. To anticipate a dropout rate of approximately 5%, 184 participants in total will be recruited. The drop-out rate is based on previous similar trials at our institution.(29, 57, 58) To handle the potential missing measurements after 1 year, the comparison of the PDI will be based on a multivariate normal model for longitudinal measurements fitted on all repeated measures over time (pre-op, postop, 4, 6, 8, 12 and 18 months). A log-transformation will be applied if necessary to handle the right-skewed distribution of the PDI.

Data analysis

Statistical analysis will be intention-to-treat and will comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarized using mean, SD, median and range values. The primary outcome will be analyzed using multilevel linear regression models for repeated (longitudinal) measures, using an unstructured covariance matrix. The mean change from baseline (i.e. preoperative assessment) to 4, 6, 8, 12 and 18 months (with correction for the postoperative assessment), will be estimated using contrast statements for each of the treatment arms. The difference in mean changes and their 95% CIs between interventions will be plotted graphically so that change can be assessed over the course of the study. Continuous secondary outcomes will be assessed in a similar way to the primary outcome. Categorical data will be analyzed using logistic models. For non-repeated continuous and binary measurements, ordinary linear regression and logistic models will be used, respectively.

Data security and management

Participant data are stored on a secure database in accordance with the General Data Protection Regulations (2018). Data is de-identified and a unique trial identification number used on all participant communication. Clinical and patient forms are being checked for completeness and congruity before data entry onto the database. Data will undergo additional checks to ensure consistency between data submitted and original paper forms. Trial documentation and data will be archived for at least 10 years after completion of the trial.

Trial monitoring

The steering committee of the research team will oversee all aspects of design, delivery, quality assurance and data analysis. The steering committee will monitor the trial at least once per year.

ETHICS AND DISSEMINATION

Ethical considerations

The EduCan Trial applies the principles established in the Declaration of Helsinki. Participants provide written informed consent before data collection. Only de-identified coded and interpreted data will be shared between the members of the research team. Ethics approval was granted by the local Ethical Committee of the University Hospitals Leuven (s60702).

Dissemination of results

The research team are committed to full disclosure of the results of the trial. Findings will be reported in accordance with CONSORT guidelines and we aim to publish in high impact journals. Given the multitude of outcome parameters, results will be divided over several papers. Our patient representatives and representative of the National Health Service will assist with dissemination of study results. The funder will take no role in the analysis or interpretation of trial results.

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AUTHORS' CONTRIBUTION

ADG, EVDG and LD drafted the manuscript. ADG, ND, MM, AS, LG, BM are the principal coordinators of the EduCan Trial. All other authors contributed to the establishment of the protocol, revised the manuscript and provided input according to their area of expertise.

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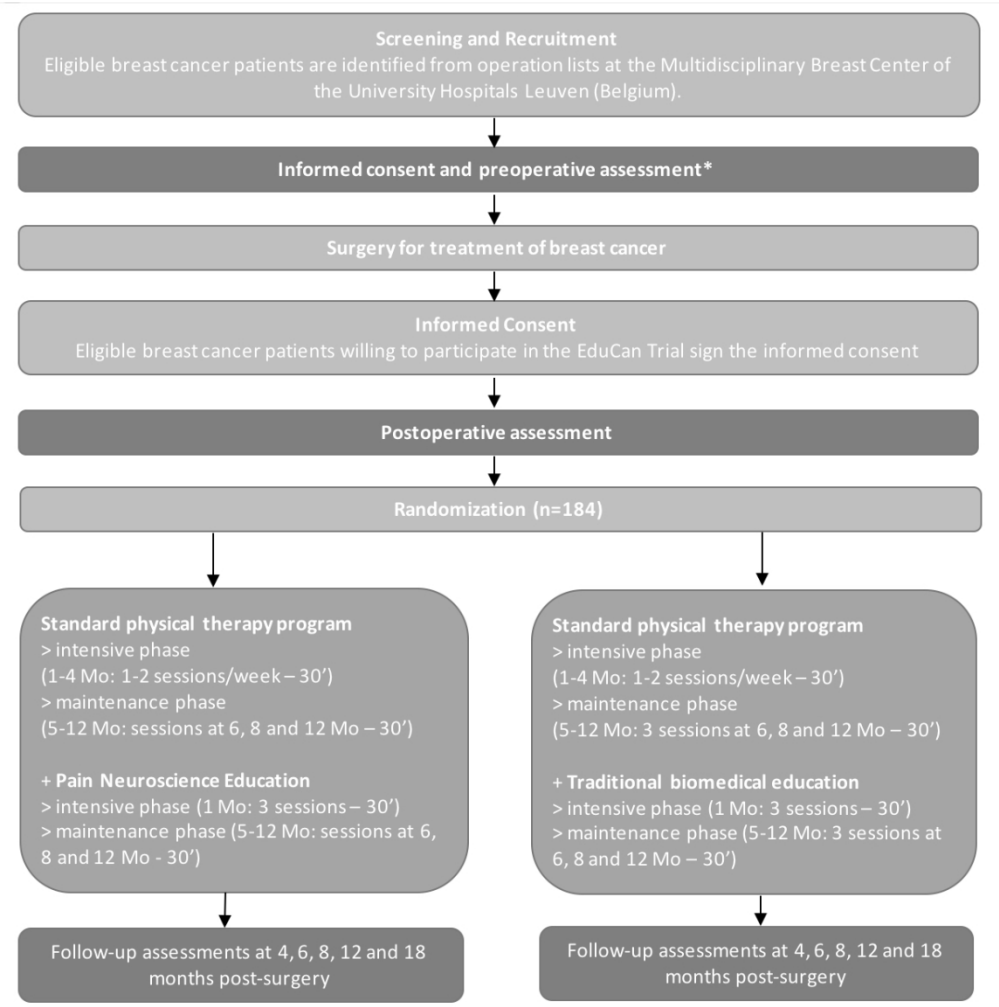
COMPETING INTERESTS STATEMENT

Nothing to declare.

FIGURE LEGEND

Figure 1: Flow diagram of the EduCan Trial

*A separate informed consent is available for the preoperative assessment
Mo=Months



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EduCan Trial: Study protocol for a randomized controlled trial on the effectiveness of Pain Neuroscience Education after breast cancer surgery on pain-, physical-, emotional- and work-related functioning

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EduCan Trial: Study protocol for a randomized controlled trial on the effectiveness of Pain Neuroscience Education after breast cancer surgery on pain-, physical-, emotional- and work-related functioning

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Abstract

Introduction:

Over the past decades, awareness on the importance of educational interventions in cancer pain management has increased. However, education is often restricted to biomedical pain management instructions. A more modern educational approach, also known as Pain Neuroscience Education (PNE), explains pain from a biopsychosocial perspective. We hypothesize that this more comprehensive educational approach in the early treatment phase of breast cancer will lead to more beneficial effects for cancer pain management. Therefore, the aim of the present study is to investigate the effectiveness of this PNE intervention, in addition to best evidence physical therapy modalities for treatment and prevention of pain-, physical-, emotional-, and work-related functioning after breast cancer surgery, compared to a traditional biomedical educational intervention.

Methods:

A double-blinded randomized controlled trial has been started in November 2017 at the University Hospitals of Leuven. Immediately after breast cancer surgery, all participants (n=184) receive a 12-week intensive standard physical therapy program. They receive three additional refresher sessions at 6, 8 and 12 months post-surgery. In addition, participants receive three educational sessions during the first month post-surgery and three 'booster sessions' at 6, 8 and 12 months post-surgery. In the intervention group, the content of the education sessions is based on the modern PNE approach. Whereas in the control group, the education is based on the traditional biomedical approach. The primary outcome parameter is pain-related disability 1 year after surgery. Secondary outcomes relate to other dimensions of pain and physical-, emotional-, and work-related functioning at 1 week, 4, 6, 8, 12 and 18 months post-surgery.

Ethics and dissemination:

The study will be conducted in accordance with the Declaration of Helsinki. This protocol has been approved by the ethical committee of the University Hospitals of Leuven. Results will be disseminated via peer-reviewed scientific journals and presentations at congresses.

Trial Registration: ClinicalTrials.gov Identifier: NCT03351075

Ethical Committee of the University Hospitals Leuven: s60702

World Health Organization Trial Registration Data Set

Data Category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT03351075
Data of registration	22 November 2017
Sponsor	University Hospitals Leuven
Contact	an.degroef@kuleuven.be; +32 16 342 171
Public title	EduCan Trial: Study protocol for a randomized controlled trial on the effectiveness of Pain Neuroscience Education after breast cancer surgery on pain-, physical-, emotional- and work-related functioning
Countries of recruitment	Belgium
Health condition	Breast cancer
Interventions	Intervention: Pain Neuroscience Education Control: Traditional biomedical education
Key inclusion criteria	Women treated for unilateral primary breast cancer
Study type	A parallel, two-arm randomized controlled trial with blinding of assessors and physical therapists
Date of first enrolment	December 2017
Target sample size	184
Recruitment status	Recruiting
Primary outcome	pain-related disability
Key secondary outcomes	pain and physical-, emotional-, and work-related functioning

Strengths and limitations of this study

- This study comprises a well-powered clinical trial investigating the additional effect of an easy deliverable Pain Neuroscience Education (PNE) intervention for pain-related disability and related outcomes following breast cancer treatment.
- A strength of the trial is the pragmatic nature of the study and applicability in daily clinical practice.
- The study is powered for the primary outcome parameter 'pain-related disability' 1 year after surgery.

INTRODUCTION

Breast cancer is the most frequent malignancy among women worldwide.(1) Despite the high incidence, in Western countries an increase in survival and life expectancy has been observed due to the ongoing improvement of detection method accuracy, early diagnosis, and breast cancer treatment.(1) Consequently, more attention is warranted towards the debilitating problems accompanying this disease and its treatment, which can persist for months or even years after diagnosis. In addition to fatigue, pain is the most frequent and persistent symptom following cancer and cancer treatment. Between 27 and 79% of women report pain one month after surgery, which is often attributed to local pain mechanisms caused by a post-surgery and/or radiotherapy tissue insult at that time-point. (2-5) One would expect prevalence rate to diminish as healing occurs, yet this does not seem to be the case. In fact, 12-82% of women still report persistent pain one year or later.(4) This may indicate that besides local nociceptive and neuropathic pain mechanisms, a third pain mechanism characterized by altered nociceptive processing without clear evidence of persistent tissue damage causing the activation of peripheral nociceptors (i.e. nociceptive pain) or evidence for disease or lesion of the somatosensory system causing the pain (i.e. neuropathic pain).(6-8) Moreover, pain interferes with pain-, physical-, emotional- and work-related disability and therefore severely prejudices a person's quality of life (QOL) and participation in society.(9-11) Hence, adequate pain management in the early stage of breast cancer treatment is necessary to prevent and improve pain and pain-related disability, both at short- and long-term.

Despite the effectiveness of currently applied physical therapy modalities after breast cancer surgery (such as manual techniques, specific exercises and general exercises), up to 72% of women still experience pain and the resulting disabilities after finishing breast cancer treatment.(12) Over the past decades, awareness on the important role of educational interventions in the management of cancer pain has increased.(13-15) These general educational interventions have been shown to be effective for improving pain severity, self-efficacy and knowledge and attitude to pain and analgesia in cancer patients. However, effect sizes are only

moderate and of limited clinical relevance.(13) This can be explained by the fact that these educational interventions mainly focus on tissue and tissue injury as the source of pain and are often restricted to biomedical pain management instructions and general advice on physical activity and analgesics.(13-15) They focus on explaining treatment side-effects and improving patients' coping strategies. Recently, increased knowledge on pain mechanisms has led to a more modern educational approach, also known as Pain Neuroscience Education (PNE).(16-19) This explains the neurophysiology of chronic pain and the ability of the nervous system to modulate pain experience, as well as the potential influences of sleep, thoughts, feelings and culture, among others, on pain. Thereby, it targets a reconceptualization from a biomedical or structural model to an actual biopsychosocial model of pain. Through the knowledge that pain is often an unreliable indicator of the presence or extent of tissue damage and if patients may become open to exploring broader contributions to pain, pain-related behavior might change by shifting from passive therapy-receiving to active self-management. Increased knowledge of the broad contributions to pain (4), as well as awareness of different pain mechanisms following breast cancer treatment (6-8) provides justification for the integration of PNE in this population. Applying PNE could enhance the effectiveness of the currently applied physical therapy modalities for prevention and treatment of pain and related disabilities after breast cancer treatment, compared to a traditional biomedical educational intervention. Indeed, encouraging people to address emotional, cognitive and broader health-related factors in the early stage of cancer treatment may enhance recovery during and after the treatment. To our knowledge, only one controlled trial investigated the effectiveness of PNE in the early stage of breast cancer treatment.(20) Although the results were very promising for shoulder function, only short-term effects were examined, no randomization was performed and no pain-related or other health-related outcomes were evaluated.

Objectives

The main scientific objective is to examine the effectiveness of PNE, in addition to a standard best evidence physical therapy program, on pain-, physical-, emotional-, and work-related functioning in the early stage of breast cancer treatment, compared to a traditional biomedical educational

intervention, up to 1.5 years after surgery (EduCan Trial). This will be performed through a double-blinded randomized controlled trial.

METHODS AND ANALYSIS

Described according to the SPIRIT guidelines (http://www.spirit-statement.org/protocol-version/).

Trial design and study setting

A parallel, two-arm randomized controlled trial with blinding of assessors and physical therapists providing the standard physical therapy program in both arms and masking of the participants. The trial started in November 2017 at the department of Physical Medicine and Rehabilitation of the University Hospitals in Leuven (Belgium). A schedule of the EduCan Trial is provided in Table 1.

Table 1. Schedule of enrolment, interventions, and assessments of the EduCan Trial

	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				
TIMEPOINT	$-t_2$ *preop consult*	$-t_1$ *postop consult*	**0**	t_1 *4 Mo*	t_2 *6 Mo*	t_3 *8 Mo*	t_4 *12 Mo*	t_5 *18 Mo*
ENROLMENT								
Eligibility screen	X							
Informed consent	X							
Randomization			X					
Allocation			X					
INTERVENTIONS								
				Intensive phase	*Maintenance phase*			
Standard PT program (All)		n=184		1-2 sessions /week	1 session	1 session	1 session	
Pain Neuroscience Education (IG)		n=92		3 sessions	1 session	1 session	1 session	
Biomedical Education (CG)		n=92		3 sessions	1 session	1 session	1 session	
ASSESSMENTS								
Pain-related functioning (primary outcome)*	X	X		X	X	X	X	X
Pain-related outcomes*	X	X		X	X	X	X	X
Emotional functioning	X	X		X	X	X	X	X
Physical functioning*		X		X			X	X
Work-related functioning*				X	X	X	X	X

*see Table 2 for details on the content of the different assessments at each point in time
Mo = Months; IG=Intervention Group; CG=Control Group

Patient and public involvement in trial design

One female breast cancer patient and a representative of the National Health Service were consulted during the initial grant preparation and trial set up. The patient representative provided valuable insight into the worries and concerns experienced during cancer treatment. The representative of the National Health service contributed to the design of the study and advised on assessment of work-related functioning outcomes.

Eligibility criteria

Women are eligible to participate in the EduCan Trial if they are scheduled for surgery for breast cancer at the Multidisciplinary Breast Center of the University Hospitals of Leuven. Patients with increased risk of developing pain after breast cancer surgery are included.(21-23) Therefore, inclusion criteria are: 1) diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, 2) scheduled for surgical excision including either axillary lymph node dissection and mastectomy (whether or not in combination with reconstructive surgery) or breast-conserving; or either sentinel node biopsy and mastectomy (whether or not in combination with reconstructive surgery); 3) aged 18 years or older; 4) can comply with the study protocol. Patients with active metastasis are excluded because of the higher risk of mortality.

Participant screening, recruitment and consent.

Participants are identified from scheduled operation lists and screened for eligibility criteria. The initial screening process is undertaken by a member of the research team. Potentially eligible participants are approached and recruited during the *preoperative consult* at the Multidisciplinary Breast Center of the University Hospitals of Leuven. All eligible patients receive an information sheet and the explanation of the study during the preoperative consult. Next, they are asked to have a preoperative baseline measurement for which a separate informed consent exists. Because of ethical and deontological reason patients will not be forced to decide

on participation in the complete EduCan Trial at this moment, but initially only for the baseline measurements.

During their *postoperative hospital stay*, a member of the research team will meet the eligible participants again, answer further questions and include them in the further trial if wanted. Then, a second informed consent is signed for participating in the complete EduCan Trial. The preoperative baseline measurement of non-participating patients will be stored in the medical file of the patient and can be consulted on clinical follow-up appointments to evaluate the recovery of the patient but is not used for research purpose. The participants' flow is summarized in Figure 1.

Allocation and randomization

Therapists and assessors are blinded to the allocation of the treatment groups. The therapists providing the standard physical therapy program will be unaware of the type of education received by the patient (PNE in the intervention group and biomedically-focused education in the control group). Consequently, they give therapy in both groups. Assessors are blinded to the maximal extent possible. With regard to this, patients are asked not to communicate with the assessors about the intervention received. Patients are masked for the allocation to the intervention/control group; they do not know which one is the experimental intervention and which one is the control intervention, however they will of course be aware of the intervention received. To reduce bias, within one participant, therapists giving the standard physical therapy program, therapists given the educational intervention and the assessors are all different persons.

At the end of the trial, the success of assessor blinding will be examined by asking whether the assessor thought the participant had received the experimental or control intervention, including the percentage of certainty (i.e. 50% certainty means a pure guess). The same will be done for patient masking. The research members performing statistical analysis will be blinded as well.

The randomization is computer-generated and is performed by using permuted blocks (size=4). An independent co-worker at the department carries out the randomization to ensure blinding of the research team. The sequence of randomization is determined by the patient's identification number, which she receives after signing informed consent. Participants are randomized in a 1:1 ratio between intervention and control arms.

Interventions

Standard physical therapy program

All participants in the EduCan Trial attend a standard physical therapy program. The standard physical therapy program is based on currently available evidence and clinical experience of the research team and will include three physical therapy modalities. Additionally, to avoid conflicts with the information given during the educational interventions, a communication sheet had been made. This document contains guidelines on which information the physical therapists can

provide on common topics discussed during the standard physical therapy sessions. First, **manual techniques** including (a) passive mobilizations to restore shoulder range of motion, (b) stretching of the pectoral muscles to improve muscle flexibility and (c) scar tissue massage to improve flexibility of the scar(s) will be implemented.(12, 24, 25) Second, **specific exercises** to improve shoulder range of motion and upper limb strength have been proven to be effective for treatment of upper limb problems after breast cancer and will start immediately after surgery as well.(12, 26) Specific exercises are instructed during the individual session and continued at home. Third, patients are advised on **general exercises.** General exercises should be implemented to increase patient's physical activity level. In general, these recommendations consist of physical activity at a minimum level of moderate intensity over an extended period and can include e.g. running, walking, cycling, swimming, etc.(27, 28)

During month 1-4 an **intensive physical therapy program** is implemented because of the postoperative side-effects. Patients will attend 1-2 individual sessions of 30 minutes per week during the intensive phase, starting one week post-surgery. All patients start with a frequency of two sessions per week, decreasing to once each two weeks. The decrease in frequency of the sessions is pragmatically chosen based on the individual progression and need of the patient.
Up to one year after surgery a **maintenance physical therapy program** is implemented to follow-up on the exercises performed at home and to treat possible additional/ new side-effects of other adjuvant treatment modalities such as radiotherapy, chemotherapy and hormone therapy. An individual maintenance session of 30 minutes is scheduled 6, 8 and 12 months post-surgery.

Additionally, **information about prevention of lymphedema** is given by a specialized physical therapist: about normal use of the upper limb, avoiding pinching off the arm, skin care and control of body weight.(29) One group information sessions of 60 minutes on this topic is organised each month which should be attended once by every participant (both patients from the intervention and control group together) and this as soon as possible after surgery. Patients also receive a brochure with this information. If patients develop lymphedema they are

additionally referred to the Lymfovenous Center of the University Hospitals of Leuven for further treatment of the lymphedema.

Educational intervention

The educational sessions are individual and last for 30 minutes. The first PNE session is given within the first postoperative week before the start of the standard physical therapy program to prepare the patient for the physical therapy sessions. Information is presented verbally (explanation by the therapist) and in multi-media forms (power point presentation with summaries, pictures, metaphors and diagrams on computer). After the first session, patients also receive an information leaflet on paper and are asked to read it carefully at home. They also receive a web-link to an online presentation that summarizes the provided information. Additional written information that can be read afterwards is a valuable and essential part of the educational intervention. In the following 4 weeks after surgery, 2 additional PNE sessions are provided to ensure that the patient understands the pain physiology and principles of activity management and can relate this to the physical therapy program and his/her pain complaint. However, education is a continuous process initiated at the start and continuing into and followed-up during the longer-term rehabilitation program. Therefore, three additional booster sessions are organized at 6, 8 and 12 months post-surgery. During the booster sessions, the information given postoperatively will be rehearsed and application of the information into future stages of the recovery process will be discussed. Special attention is given to return to preoperative activities and return to work (if applicable). Regarding this, a second information leaflet on paper will be given to the patient. Patients in the control arm and intervention arm will have the same schedule of educational sessions, only the content of the education differs from the intervention arm.

Intervention arm: Pain Neuroscience Education (PNE)

Based on the available literature a modern PNE program has been established to *explain pain* specifically for this population.(13, 15, 20) The content and pictures of the educational sessions are based on the book 'Explain Pain' (Butler & Moseley, 2003), 'Pijneducatie een praktische

handleiding voor (para)medici' (Van Wilgen & Nijs, 2011) and the 'The Pain Toolkit' (Peter Moore, 2002), as used in earlier studies.(30, 31) Topics addressed during the PNE sessions will include: the characteristics of acute versus chronic pain; specific side effects of the different breast cancer treatment modalities in relation to pain; how pain is a product of the brain; how pain becomes chronic (plasticity of the nervous system, modulation, modification, central sensitization); potential sustaining factors of pain such as emotions, stress, pain cognitions, and pain behavior. Additionally, this PNE intervention includes advice for *activity management*, while experiencing pain and other symptoms. In addition to the general recommendations for general exercise and advice to stay active in the standard physical therapy program, the PNE guides patients in performing general exercises and activities according to the graded activity principle. Graded activity is applied according to the guidelines reported by the International Association for the Study of Pain (IASP).(32) This includes general exercise activities according to pacing strategies for 'persisters' (i.e. restructuring the activity pattern to avoid peaks of over activity and exacerbations of their pain) and graded activity for 'avoiders' (i.e. time-contingent increase of physical activity). PNE is crucial here to help patients interpret pain during exercise in the correct context. Finally, advice on *returning to work* in the context of present pain complaints and how to apply the principles described above for activity management can be applied in the working situation will be provided.

Control arm: Traditional biomedical education

Traditional biomedical educational interventions consist of *explaining patient's pain* experience in relation to the therapeutic procedures from a tissue and biomechanical perspective.(33, 34) Information on the different side effects of surgery, radiotherapy, chemotherapy, hormone therapy and target therapy is given. The role of different structures and injured versus healthy tissue in acute and persistent pain is discussed. Pain is explained from a biomechanical point of view, e.g. deviance from normal expected movement patterns and postures. Additionally, during the educational sessions and rehabilitation program, patients receive advice on activity management. This advice is to stay active as minimally possible during treatment and increase their *physical activity* level according to current recommendations for general exercises after

treatment. Based on the American Cancer Society Guidelines on Physical Activity at least 150 minutes of moderate intensity (heart rate 50 to 70% of the maximum heart rate or a score of 12-14 on Borg Rating of Perceived Exertion (RPE)) or 75 minutes of vigorous intensity activity (70 to 85% of the maximum heart rate or RPE of > 15) each week (or a combination of these), preferably spread throughout the week is recommended. Finally, *advice on returning to work* in the context of the different (persistent) side-effects of the treatments will be provided.

Outcomes

The outcome measures were chosen in accordance with the guideline for **core outcome domains** to be used in clinical trials on multimodal treatment approaches for pain as advocated by an international steering committee (**VAPAIN recommendations**)(35) and the **IMMPACT recommendations** for the outcome measures in pain clinical trials.(36)

The primary outcome is pain-related functioning at 12 months measured using the Pain Disability Index (PDI). Secondary outcomes are other pain symptoms and characteristics, physical functioning, emotional functioning and work-related functioning. Additionally, number of visits are recorded. Assessments are performed within one week preoperatively, within one week postoperatively and then at 4 months, 6, 8, 12 and 18 months after surgery. However, because of feasibility limitations not all outcome parameters are assessed at each assessment time point. Table 1 and 2 present the study outcome measures by assessment time point. In table 3 the outcome measures are described in more detail.

Table 2. Study outcome measures by assessment time point

Domain	**Scale/measure**	**T_{-2} 1W preop**	**T_{-1} 1W postop**	**T_1 4 Mo**	**T_2 6 Mo**	**T_3 8 Mo**	**T_4 12 Mo**	**T_5 18 Mo**
Pain-related functioning (primary outcome)	Pain Disability Index	x	x	x	x	x	x	x
Pain symptoms and characteristics	Pain intensity (VAS)	x	x	x	x	x	x	x
	Brief Pain Inventory (BPI)	x	x	x	x	x	x	x
	Neuropathic Pain Questionnaire (DN4)	x	x	x	x	x	x	x
	Central Sensitisation Questionnaire (CSI)	x	x	x	x	x	x	x
	Pain sensitivity testing	x	x	x	x	x	x	x

Physical functioning	General physical activity level (accelerometry)		x	x			x	x
	Upper limb performance (accelerometry)		x	x			x	x
	Upper limb function (DASH)	x	x	x	x	x	x	x
Emotional functioning	Pain Catastrophizing Scale (PCS)	x	x	x	x	x	x	x
	Depression, Anxiety and Stress Scale (DASS-21)	x	x	x	x	x	x	x
	Health-related quality of life (McGill Quality of life questionnaire)	x	x	x	x	x	x	x
Social functioning	Return to work rate			x	x	x	x	x
	QuickScan			x	x	x	x	x
	Return-to-work self-efficacy (RTWSE-19)			x	x	x	x	x

Table 3. Outcome measures of the EduCan Trial

Outcome	Assessment method
PAIN-RELATED FUNCTIONING (primary outcome)	
Pain-related functioning	Pain Disability Index (PDI). The PDI is a short, self-reported questionnaire for measuring the degree of interference of pain with normal role functioning (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity).(37, 38)
PAIN SYMPTOMS AND CHARACTERISTICS	
Pain intensity	Visual Analogue Scale (VAS). Present pain intensity and mean pain intensity during the past week for pain at the upper limb region (i.e. shoulder-neck region, arm, axilla, trunk side and breast region)
Brief Pain Inventory	Medication use, pain quality, pain location, pain severity and response to treatment.(39)
Presence of neuropathic pain	Douleur Neuropathique en 4 questions (DN4). The DN4 a questionnaire generating reliable and valid data for identifying pain of predominantly neuropathic origin.(40)
Presence of hypersensitivity of the central nervous system	Central Sensitisation Inventory (CSI). The CSI is a questionnaire generating reliable and valid data to assess symptoms related to central sensitization mechanisms.(41)
Pain sensitivity testing	
*- Quantitative Sensory testing: Mechanical detection and pain thresholds**	*Twelve monofilaments (MARSTOCK nerve test - Optihair2, Schriesheim, Germany) with a force from 0.25 to 512 mN are used. The mechanical detection threshold is defined as the lowest mechanical force that the participant can detect. The mechanical pain threshold is defined as the lowest mechanical force that the participant perceives as painful or unpleasant. Monofilaments are applied with a rate of 2 seconds 'on' and 2 seconds 'off' at the inner side of the upper arm and lateral trunk side.*
*- Quantitative Sensory testing: Temperature detection and pain thresholds**	*The computerized thermotest device TSA-II-NeuroSensory Analyser is used. The method of limits is used. The detection and pain thresholds are measured as the first identified stimulus under increasing stimulus intensities. The participant has to push the button once the stimulus is detected or perceived as painful or unpleasant. This is repeated three times for each threshold. The mean of three stimuli for each threshold is calculated and used for analysis.(42).*
*- Quantitative Sensory testing: Pressure Pain Thresholds**	*Measured by a digital Wagner FPX™ algometer. Points of measurement are defined by palpation for most tender muscle points (one per muscle) at the major pectoral muscle region, the lateral trunk side and upper trapezius muscle region. The participant is asked to say 'stop' when the sensation of pressure first changes to pain. The mean value of the 2 measurements is calculated and used for analysis.(43)*
- Presence of widespread pain/secondary hyperalgesia	*Quantitative Sensory Testing is performed both at the local painful area as at remote body parts (i.e. quadriceps muscle at the non-affected side) and pain distribution is displayed on a body diagram*

- Presence and degree of impaired nociceptive inhibitory mechanisms (i.e. conditioned pain modulation)	*Assessment of conditioned pain modulation will be done using the Medoc two thermode Q-Sense CPM system. This system involves a 'test' stimulus and a 'conditioning' stimulus applied on the ulnar side of the forearms. The test stimulus (at the affected side) is used to assess pain sensitivity to a warmth stimulus pre- and post the noxious conditioning stimulus and the difference is calculated between pre- and post-measures. When the second pressure pain threshold (i.e. test stimulus) is similar or lower than the first, dysfunctional inhibitory pain mechanisms are present.(44, 45)*
- Presence and degree of enhanced facilitation mechanisms (i.e. wind-up)	*Wind-up of pain or temporal summation will be assessed by applying repetitive nociceptive stimulation with a 26g Nylon monofilament at the major pectoral muscle at the affected side. The perceived intensity of the stimulus (the first, the last and aftersensations) are reported by using a Numeric Rating Scale. The temporal summation value is calculated as the difference between the first and the last stimuli or the slope of the increase in pain intensity. A response for enhanced temporal summation is deemed positive if participants perceive the initial stimulus as non-noxious, but it becomes noxious, increasing by at least two-points on a Numeric Rating Scale, or if baseline pain intensity increases by at least two points.(44-46)*
- Presence and degree of hypersensitivity to non-mechanical stimuli	*The Central Sensitization Inventory, a questionnaire generating reliable and valid data to assess symptoms related to central sensitization mechanisms (47-49)*
PHYSICAL FUNCTIONING	
General physical activity and upper limb performance	Three ActiLife accelerometers, one on the pelvis (7 consecutive days) and one on each wrist (3 consecutive days), will be worn during waking hours. Outcome parameters are general activity level, unimanual/bimanual time and intensity of both unimanual/bimanual use. The ActiLife v6.9.5 Firmware v2.2.1 will be used to save raw data. Data will be further processed with Matlab®, using custom-written routines.(50, 51)
Upper limb function	DASH questionnaire. The DASH is a self-reported questionnaire on upper limb function.(3)
EMOTIONAL FUNCTIONING	
Pain catastrophizing	Pain Catastrophizing scale (PCS). The PCS is a self-reported questionnaire measuring catastrophic thinking related to pain. (52)
Depression, anxiety and stress	Depression Anxiety Stress scales 21 (DASS-21). The DASS-21 is a self-reported questionnaire that measures the three related states of depression, anxiety and stress. (53)
Health-related quality of life	McGill Quality of Life questionnaire (54)
SOCIAL FUNCTIONING	
Return to work rate	Self-reported questionnaire on return to work, employment status, work adjustments
QuickScan	Questionnaire on health status and return-to-work obstacles in order to assess potential predictive factors for long-term absenteeism.

Patients perceived ability to work	Return-to-work self-efficacy questionnaire (RTWSE-19). The RTWSE-19 is a self-reported questionnaire on the patients' perceived ability to work.(55)

* Testing is performed bilaterally, except preoperatively because of feasibility reasons

Sample size

A power calculation was performed by the Leuven Biostatistics and statistical bioinformatics Centre of KU Leuven for the primary outcome parameter 'Pain Disability Index (PDI) after 1 year''. Sample size calculation was based on data available in literature for the PDI.(37, 38) and calculated to detect with 80% power a difference of 20% in Pain Disability Index after 1 year. Assuming a coefficient of variation (CV) equal to 0.5, 87 participants per group are needed based on a two-sample pooled t-test of a mean ratio with lognormal data and setting alpha equal to 0.05. The assumed CV is a conservative estimate, derived from the observed CV of 0.30 in a sample of normative data for women with chronic pain. To anticipate a dropout rate of approximately 5%, 184 participants in total will be recruited. The drop-out rate is based on previous similar trials at our institution.(29, 56, 57) To handle the potential missing measurements after 1 year, the comparison of the PDI will be based on a multivariate normal model for longitudinal measurements fitted on all repeated measures over time (pre-op, postop, 4, 6, 8, 12 and 18 months). A log-transformation will be applied if necessary to handle the right-skewed distribution of the PDI.

Data analysis

Statistical analysis will be intention-to-treat and will comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analysis will be conducted in a blinded way. The continuous data will be summarized using mean, SD, median and range values. The primary outcome will be analyzed using multilevel linear regression models for repeated (longitudinal) measures, using an unstructured covariance matrix. The mean change from baseline (i.e. preoperative assessment) to 4, 6, 8, 12 and 18 months (with correction for the postoperative

assessment), will be estimated using contrast statements for each of the treatment arms. The difference in mean changes and their 95% CIs between interventions will be plotted graphically so that change can be assessed over the course of the study. Continuous secondary outcomes will be assessed in a similar way to the primary outcome. Categorical data will be analyzed using logistic models. For non-repeated continuous and binary measurements, ordinary linear regression and logistic models will be used, respectively.

Data security and management

Participant data are stored on a secure database in accordance with the General Data Protection Regulations (2018). Data is de-identified and a unique trial identification number used on all participant communication. Clinical and patient forms are being checked for completeness and congruity before data entry onto the database. Data will undergo additional checks to ensure consistency between data submitted and original paper forms. Trial documentation and data will be archived for at least 10 years after completion of the trial.

Trial monitoring

The steering committee of the research team will oversee all aspects of design, delivery, quality assurance and data analysis. The steering committee will monitor the trial at least once per year.

ETHICS AND DISSEMINATION

Ethical considerations

The EduCan Trial applies the principles established in the Declaration of Helsinki. Participants provide written informed consent before data collection. Only de-identified coded and interpreted data will be shared between the members of the research team. Ethics approval was granted by the local Ethical Committee of the University Hospitals Leuven (s60702).

Dissemination of results

The research team are committed to full disclosure of the results of the trial. Findings will be reported in accordance with CONSORT guidelines and we aim to publish in high impact journals. Given the multitude of outcome parameters, results will be divided over several papers. Our patient representatives and representative of the National Health Service will assist with dissemination of study results. The funder will take no role in the analysis or interpretation of trial results.

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AUTHORS' CONTRIBUTION

ADG, EVDG and LD drafted the manuscript. ADG, ND, MM, AS, LG, BM, KB, NM, PVW are the principal coordinators of the EduCan Trial and designed the protocol. All other authors contributed to the establishment of the protocol, revised the manuscript and provided input according to their area of expertise.

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COMPETING INTERESTS STATEMENT

Nothing to declare.

FIGURE LEGEND

Figure 1: Flow diagram of the EduCan Trial

*A separate informed consent is available for the preoperative assessment
Mo=Months

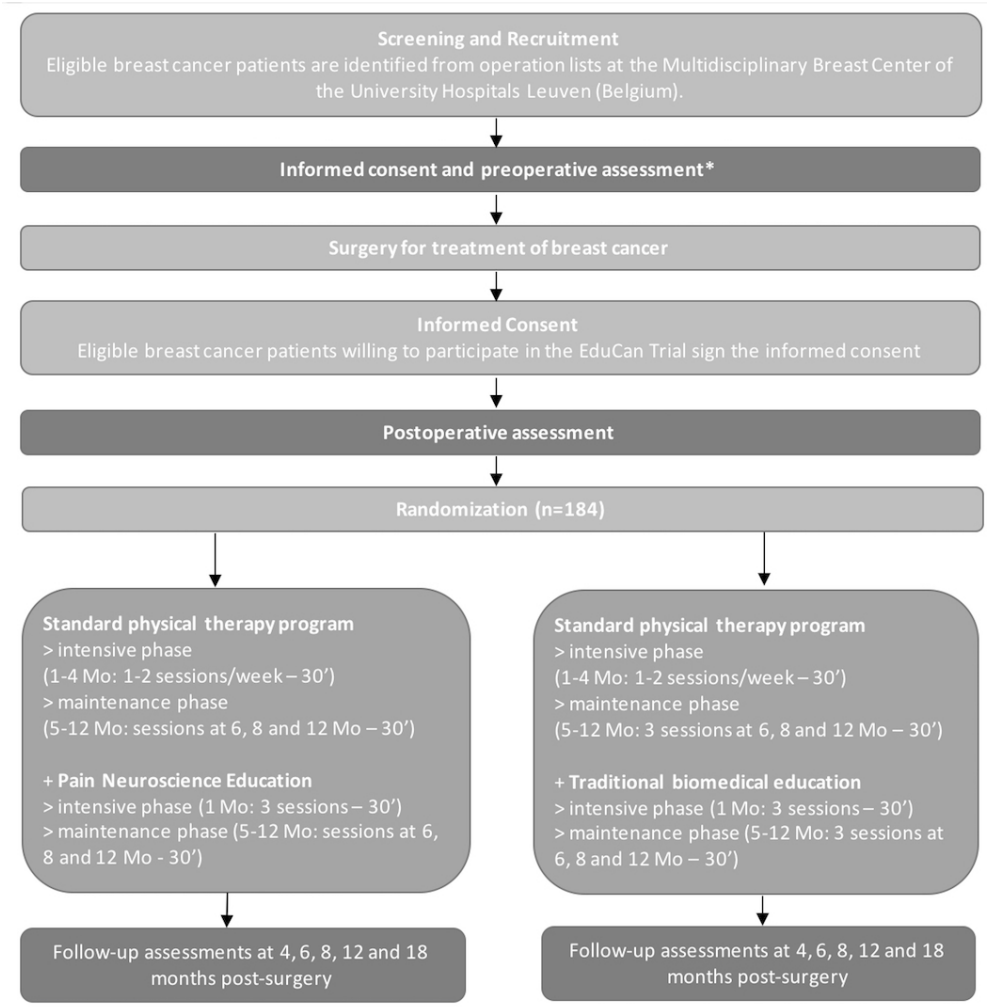

Figure 1: Flow diagram of the EduCan Trial
*A separate informed consent is available for the preoperative assessment
Mo=Months

90x91mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	p.3
Protocol version	3	Date and version identifier	p.3
Funding	4	Sources and types of financial, material, and other support	p. 26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1
	5b	Name and contact information for the trial sponsor	p.1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 5-6
	6b	Explanation for choice of comparators	p. 5-6

Objectives	7	Specific objectives or hypotheses	p. 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 15 table 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p.19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p.11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p.20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p.20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p.20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p.20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.21

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p.21
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	p.21
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p.21
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.